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L3: Entry 50 of 50 File: USPT Feb 28, 1989

US-PAT-NO: 4808314
DOCUMENT-IDENTIFIER: US 4808314 A

TITLE: Method for reducing bacterial endotoxin contamination in solutions of macromolecules

DATE-ISSUED: February 28, 1989

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Karplus; Thomas E.	Sydney			AUX
Ulevitch; Richard J.	Del Mar	CA		
Wilson; Curtis B.	San Diego	CA		

US-CL-CURRENT: 210/638; 210/639, 210/647, 210/649

CLAIMS:

What is claimed is:
1. A method of reducing a bacterial endotoxin contaminant in an aqueous composition containing a biologically useful macromolecule comprising the steps of:
(a) admixing an endotoxin-contaminated biologically useful macromolecule with a dialyzable surfactant in an aqueous medium to form an aqueous admixture, said surfactant exhibiting no net electric charge at the pH value of said aqueous admixture and being present in said admixture at a concentration greater than said surfactant's critical micelle concentration;
(b) contacting said aqueous admixture with a water-insoluble solid phase endotoxin sorbant comprising a solid phase matrix linked to an endotoxin sorbing agent to form a solid-liquid phase admixture;
(c) maintaining said contact for a time period sufficient for said endotoxin to bind to said sorbant and form a second solid-liquid phase admixture whose liquid phase contains water, said macromolecule and a reduced weight ratio of endotoxin to macromolecule as compared to the weight ratio present in said aqueous admixture;
(d) separating the solid and liquid phases of said second solid-liquid phase admixture;
(e) dialyzing said surfactant from said liquid phase at a time no earlier than step (c) to provide a liquid phase that contains said macromolecule and is substantially free of surfactant; and
(f) thereafter recovering the liquid phase that is substantially free from surfactant.
2. The method according to claim 1 wherein said dialysis step is carried out after step (d).
3. The method according to claim 2 wherein said contacting, maintaining and separating of steps (b), (c) and (d) are carried out in a column.
4. The method according to claim 1 wherein said dialysis step is carried out during said maintenance step (c).
5. The method according to claim 1 wherein said endotoxin sorbing agent is polymixin B.
6. The method according to claim 1 wherein said water-insoluble matrix is

particulate.
7. The method according to claim 1 wherein said surfactant has a critical micelle concentration of at least about 0.2 weight percent or at least about 5 millimolar.
8. The method according to claim 1 wherein said surfactant is selected from the group consisting of 3-[(3-cholamidopropyl)-dimethylammonio]-1-propanesulfonate, 3-[(3-cholamidopropyl)dimethylamminio]-2-hydroxy-1-propanesulfonate; N-octyl-N,N-dimethyl-3-ammonio-1-propanesulfonate, N-decyl-N,N-dimethyl-3-ammonio-1-propanesulfonate, octyl-beta-D-glucopyranoside, octyl-beta-D-thioglucopyranoside, octanoyl-N-methylglucamide, nonoyl-N-methylglucamide and decanoyl-N-methylglucamide.
9. The method according to claim 1 wherein said surfactant is nonionic.
10. The method according to claim 9 wherein said surfactant is selected from the group consisting of octyl-beta-D-glucopyranoside, octyl-beta-D-thioglucopyranoside, octanoyl-N-methylglucamide, nonoyl-N-methylglucaimide and decanoyl-N-methylglucamide.
11. A method of reducing a bacterial endotoxin contaminant in an aqueous composition containing a biologically useful macromolecule comprising the steps of:
(a) admixing an endotoxin-contaminated biologically useful macromolecule with a surfactant in an aqueous medium to form an aqueous admixture, said surfactant exhibiting no net electric charge at the pH value of said admixture and being present in said admixture at a concentration greater than said surfactant's critical micelle concentration;
(b) contacting said aqueous admixture with a water-insoluble solid phase endotoxin sorbant comprising a solid phase matrix linked to an endotoxin sorbing agent to form a solid-liquid phase admixture;
(c) maintaining said contact for a time period sufficient for said endotoxin to bind to said sorbant and form a second solid-liquid phase admixture whose liquid phase contains water, said surfactant, said macromolecule and a reduced weight ratio of endotoxin to macromolecule as compared to the weight ratio present in said aqueous admixture;
(d) separating the solid and liquid phases of said second solid-liquid admixture;
(e) dialyzing the surfactant out of said separated liquid phase to provide a liquid phase that is substantially free of surfactant; and
(f) recovering said substantially surfactant-free liquid phase.
12. The method according to claim 11 wherein said solid phase sorbant is particulate.
13. The method of claim 12 wherein said contact is substantially continual and is maintained by agitation of said particulate sorbant.
14. The method according to claim 11 wherein said surfactant has a critical micelle concentration of at least about 0.2 weight percent or at least about 5 millimolar.
15. The method according to claim 11 wherein said surfactant is nonionic.
16. The method according to claim 15 wherein said surfactant is selected from the group consisting of octyl-beta-D-glucopyranoside, octyl-beta-D-thioglucopyranoside, octanoyl-N-methylglucamide, nonoyl-N-methylglucaimide and decanoyl-N-methylglucamide.
17. The method according to claim 11 wherein said macromolecule is present in said aqueous admixture at a concentration of about 200 micrograms per milliliter to about 100 milligrams per milliliter.
18. The method according to claim 11 wherein said aqueous medium has an ionic strength less than about 2 molar.
19. A method of reducing a bacterial endotoxin contaminant in an aqueous composition containing a biologically useful macromolecule comprising the steps of:
(a) admixing an endotoxin-contaminated biologically useful macromolecule with a surfactant in an aqueous medium to form an aqueous admixture, said surfactant exhibiting no net electric charge at the pH value of said admixture and being present in said admixture at a concentration greater than said surfactant's critical micelle concentration;
(b) contacting said aqueous admixture with a water-insoluble solid phase endotoxin sorbant comprising a solid phase matrix linked to an endotoxin sorbing agent to form a solid-liquid phase admixture;

(c) maintaining said contact while dialyzing said solid-liquid phase admixture for a time period sufficient for said endotoxin to bind to said sorbant and form a second solid-liquid phase admixture whose liquid phase contains water, said macromolecule, a reduced weight ratio of endotoxin to macromolecule as compared to the weight ratio present in said aqueous admixture, and is substantially free of said surfactant;
(d) separating the solid and liquid phases of said second solid-liquid admixture; and
(e) recovering said separated liquid phase.
20. The method according to claim 19 wherein said solid phase sorbant is particulate.
21. The method of claim 19 wherein said contact is substantially continual and is maintained by agitation of said particulate sorbant.
22. The method according to claim 19 wherein said surfactant has a critical micelle concentration of at least about 0.2 weight percent or at least about 5 millimolar.
23. The method according to claim 19 wherein said surfactant is nonionic.
24. The method according to claim 19 wherein said surfactant is selected from the group consisting of octyl-beta-D-glucopyranoside, octyl-beta-D-thioglucopyranoside, octanoyl-N-methylglucamide, nonoyl-N-methylglucaimide and decanoyl-N-methylglucamide.
25. The method according to claim 19 wherein said macromolecule is present in said aqueous admixture at a concentration of about 200 micrograms per milliliter to about 100 milligrams per milliliter.
26. The method according to claim 19 wherein said aqueous medium has an ionic strength less than about 2 molar.
27. The method according to claim 19 wherein said sorbant is monolithic, is comprised of a dialysis membrane having said endotoxin sorbing agent linked to the surface contacted by said liquid phase, and said contact is provided by flow of the liquid phase across said sorbing agent-containing surface.

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L3: Entry 50 of 50 File: USPT Feb 28, 1989

DOCUMENT-IDENTIFIER: US 4808314 A
TITLE: Method for reducing bacterial endotoxin contamination in solutions of macromolecules

BSPR:
Duff et al., Clinical Research, 30, 565A (1982) report an affinity chromatography endotoxin removal method using PMB. Briefly, polymyxin B (PMB) linked to activated Sepharose 4B was admixed with endotoxin dissolved in pyrogen-free water or saline, and the resulting admixture was agitated until equilibrium was reached. At least ninety percent of the endotoxin was reportedly retained on the PMB-coupled resin. The Duff et al. method separates solutions of pyrogen-free water or saline from added LPS. The method was not used with solutions of macromolecules and LPS. Further, the authors do not state that the procedure is suitable for removing endotoxin from solutions of macromolecules.

BSPR:
Issekutz, J. Immunological Methods, 61:275-281 (1983), reports a similar method using PMB linked to Sepharose 4B as an affinity sorbant for LPS. Issekutz also uses the sorbant to separate LPS from solutions of small molecules such as salt or serum-free tissue culture medium and additionally shows a single example in which endotoxin is separated from tissue culture medium containing 10% serum. Issekutz states that the presence of serum did not alter the effectiveness of endotoxin removal.

BSPR:
As described hereinafter, solutions that contained the enzyme catalase contaminated with endotoxin were treated by affinity chromatography with PMB-linked Sepharose 4B following the Issekutz procedure. The resulting catalase-containing solution contained approximately one-half of the protein of the original solution and about 7 to 12 percent of the original endotoxin. The remaining approximately ten percent of the endotoxin was closely associated with the enzyme and remained associated with the enzyme through subsequent PMB-Sepharose 4B treatments. It is therefore believed that the less efficient endotoxin removal from a protein-containing solution is due to endotoxin that is complexed with the protein in the serum.

BSPR:
The patent broadly discloses "unmasking" the endotoxins by treatment with salt, detergents, or organic chemical solutions, such as 2% Tween-80, 2% dextran sulfate, 3% sodium chloride, or 2% ammonium thiocyanate, and preferably benzamidine. The sole actual example of the Firca et al. patent utilizes 0.002M solutions of benzamidine or its biologically compatible acid addition salts. Those solutions are admixed with the body fluid and separated from the body fluid by affinity chromatography. "Unmasked" endotoxins adhere to the column and are eluted with strong detergent or salt solutions, such as 2% sodium dodecyl sulfate (SDS), 3% sodium deoxycholate, or 2M MgCl. Eluted endotoxins are precipitated with alcohol and detected by known methods.

DRPR:
The term "free from net electric charge" and its equivalent phrases is used herein to mean that the surfactant is electrically neutral at the stated pH value. Thus, the surfactant can be nonionic, as is preferred, or can be

zwitterionic where the positive and negative charges are balanced, but cannot be anionic as is the case of SDS or a bile acid, nor cationic as in the case of a quaternary amine-containing surfactant.

DRPR:
Another way of assessing dialyzability is by use of a standard assay. A useful assay is similar to that utilized herein for endotoxin removal, but is carried out in the absence of the macromolecule and endotoxin sorbant. Thus, the surfactant is dispersed in about 40 ml of phosphate-buffered saline (PBS) at a surfactant concentration of about four-times the cmc of the surfactant, e.g., for OBDG at about 100 mM. That 40 ml of liquid is placed in a Spectrophor dialysis bag with a 12,000-14,000 molecular weight exclusion. The bag and its contents are then placed in a closed 2-liter container filled with PBS as dialyzing fluid, and the container and bag are subjected to constant agitation for a time period of 48 hours at ambient room temperature (20-22 degrees C.), with at least four changes of dialyzing fluid made at about evenly spaced intervals during the 48 hours.

DRPR:
The amount of surfactant remaining in the bag is thereafter determined. If the surfactant remaining in the solution in this assay is not more than about 2 percent of that originally present; i.e., 2 percent of an amount that is four-times the surfactant cmc value, the surfactant can be said to be dialyzable for the purposes of this invention and the aqueous liquid containing that amount of surfactant can be said to be substantially free of surfactant. For example, using OBDG at an initial concentration of 100 mM (2.94 weight percent), an average value of 0.016 weight percent was found after endotoxin removal, or about 0.5 weight percent of the originally present amount.

DRPR:
Solutions of SDS are reported to remove LPS from polymixin B affixed to a solid matrix. SDS is a well known protein denaturant and for that reason alone is not useful herein. In addition, SDS was found to dialyze poorly out of a solution under conditions otherwise found useful herein, and it therefore appears that the SDS cmc value is nearer to the 0.015 value shown in Table 1 than it is to the 0.23 weight percent value also shown in that Table under the conditions usually used herein.

DRPR:
A preferred particulate solid phase matrix is cross-linked agarose. Particularly preferred is a cross-linked agarose such as cyanogen bromide-activated Sepharose 4B (Pharmacia Fine Chemicals, Piscataway, N.J.) which is readily linked to PMB to form the solid phase sorbant. An exemplary 5 ml volume of polymyxin B-Sepharose 4B (PB-Seph4B) is capable of adsorbing about 12 mg of endotoxin, which is far in excess of the amount of endotoxin present in all but the most contaminated macromolecule solutions. Further, the sorbant can be backwashed with, for example, strong detergents such as a 1 percent SDS solution or a 1-3 percent sodium deoxycholate to restore the ability to bind endotoxin. Thus the sorbant can be reused.

DRPR:
As is discussed hereinafter, use of polymyxin B linked to Sepharose 4B as discussed above, without a surfactant, during dialysis failed to adequately reduce the endotoxin concentration in LPS-contaminated protein solutions. This result, which utilized techniques similar to those described by others and discussed hereinbefore, and the results with dialysis suggest that binding of endotoxin to protein may limit the capacity of sorbant systems alone, and even when coupled with simultaneous dialysis, to efficiently clear endotoxins from such solutions. None of the previously described methods for decontaminating protein solutions address the problem of inaccessibility of macromolecule-bound endotoxin to removal by affinity sorbant chromatography methods, regardless of the solid phase sorbant employed.

DRPR:
Following endotoxin reduction in accordance with this invention, the solid phase

PMB-Sepharose 4B sorbant was treated with a 1 percent SDS solution to remove bound LPS. The counts that were removed from a macromolecule-LPS admixture were eluted (97.4 percent) from the sorbant, demonstrating that the balance of the LPS was bound to the sorbant. Results from additional studies showed that the solid phase PMB-Sepharose 4B sorbant that had been freed of bound endotoxin by the SDS treatment could be successfully reused for additional endotoxin removal.

DRPR:
The chromatography approach used a higher ratio of PB-Seph 4B to catalase than the dialysis method. When the ratio was reduced by decreasing the amount of sorbant placed in the column, the amount of LAL reactivity removed decreased below a volume of 0.4 ml of sorbant; i.e., 0.2 ml in the same diameter column, decreased the LAL reactivity by only 100-fold. It is thought that the observed decrease in endotoxin removal was due to a relatively shorter contacting time between the sorbant and aqueous admixture.

DRPR:
The sorbant-containing solid phase was then admixed with a 1 percent SDS solution to form a second solid-liquid phase admixture that was maintained (incubated) at room temperature overnight. Following separation of the liquid and solid phases by centrifugation, the liquid phase was again assayed for beta-counts. Elution of the counts from the sorbant by SDS treatment demonstrated that the balance of the LPS had been bound to the polymyxin B-Sepharose matrix.

US-PAT-NO: 6180596
DOCUMENT-IDENTIFIER: US 6180596 B1

TITLE: Methods of inhibiting phospholipase A2 and phospholipase A2 stimulator activities

DATE-ISSUED: January 30, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Tsao; Francis H. C.	Madison	WI		

US-CL-CURRENT: 514/2; 435/18, 435/198, 514/12, 530/350, 530/380, 530/381

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Search Results - Record(s) 1 through 10 of 50 returned.

1. Document ID: US 6310186 B1

L3: Entry 1 of 50 File: USPT Oct 30, 2001

US-PAT-NO: 6310186
DOCUMENT-IDENTIFIER: US 6310186 B1

TITLE: Purification of biological preparations

DATE-ISSUED: October 30, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Wilson; Mark Jonathon	Cottenham, Cambridge, CB4 8SW			GBX
Johnston; Michael Denis	Impington, Cambridge CB4 9NY			GBX
Glenn; Deirdre Anne	Milton, Cambridge, CB4 6ZG			GBX
Gallagher; Sean Patrick	Chesterton, Cambridge, CB4 1UH			GBX

US-CL-CURRENT: 530/412; 210/198.2, 210/651, 530/351, 530/371, 530/415, 530/417, 536/123.1, 536/23.1, 536/25.4

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw Desc | Image

2. Document ID: US 6297371 B1

L3: Entry 2 of 50 File: USPT Oct 2, 2001

US-PAT-NO: 6297371
DOCUMENT-IDENTIFIER: US 6297371 B1

TITLE: Process for the preparation of endotoxin-free or endotoxin-depleted nucleic acids and/or oligonucleotides for gene therapy

DATE-ISSUED: October 2, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Colpan; Metin	Essen			DEX
Schorr; Joachim	Dusseldorf			DEX
Moritz; Peter	Kerpen			DEX

US-CL-CURRENT: 536/25.3; 435/259, 435/267, 435/268, 435/269, 435/270, 435/6, 435/810, 536/23.1, 536/25.31, 536/25.4, 536/25.41, 536/25.42

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw Desc | Image

3. Document ID: US 6297367 B1

L3: Entry 3 of 50 File: USPT Oct 2, 2001

US-PAT-NO: 6297367
DOCUMENT-IDENTIFIER: US 6297367 B1

TITLE: Polynucleotide encoding TNFL1

DATE-ISSUED: October 2, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Tribouley; Catherine	San Francisco	CA		

US-CL-CURRENT: 536/23.5; 435/252.3, 435/320.1, 435/69.1, 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw Desc | Image

4. Document ID: US 6270970 B1

L3: Entry 4 of 50 File: USPT Aug 7, 2001

US-PAT-NO: 6270970
DOCUMENT-IDENTIFIER: US 6270970 B1

TITLE: Mixed-bed solid phase and its use in the isolation of nucleic acids

DATE-ISSUED: August 7, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Smith; Craig E.	Oregon	WI		
Holmes; Diana L.	Crystal Lake	IL		
Simpson; Daniel J.	Middleton	WI		
Katzenhendler; Jehoshua	Jerusalem	IL		
Bitner; Rex M.	Cedarburg	WI		
Grosch; Josephine C.	Mazomainie	WI		

US-CL-CURRENT: 435/6; 435/803, 436/17, 530/334

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWMC | Draw Desc | Image

5. Document ID: US 6268492 B1

L3: Entry 5 of 50 File: USPT Jul 31, 2001

US-PAT-NO: 6268492
DOCUMENT-IDENTIFIER: US 6268492 B1

TITLE: Methods for purifying non-chromosomal nucleic acid molecules from cells

DATE-ISSUED: July 31, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Mittelstaedt; Denice M.	San Diego County	CA		
Hsu; David Chi-Tang	San Diego County	CA		

US-CL-CURRENT: 536/25.4; 536/26.43

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw. Desc | Image

☐ 6. Document ID: US 6231854 B1

L3: Entry 6 of 50 File: USPT May 15, 2001

US-PAT-NO: 6231854
DOCUMENT-IDENTIFIER: US 6231854 B1

TITLE: Methioninase formulations and use in diagnostic methods

DATE-ISSUED: May 15, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Yuying; Tan	San Diego	CA		

US-CL-CURRENT: 424/94.5; 424/94.2, 435/188, 435/232

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw. Desc | Image

☐ 7. Document ID: US 6222021 B1

L3: Entry 7 of 50 File: USPT Apr 24, 2001

US-PAT-NO: 6222021
DOCUMENT-IDENTIFIER: US 6222021 B1

TITLE: Fragments of endotoxin binding protein and uses thereof

DATE-ISSUED: April 24, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Wainwright; Norman R.	Falmouth	MA		
Novitsky; Thomas J.	E. Falmouth	MA		

US-CL-CURRENT: 530/395; 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 8. Document ID: US 6194562 B1

L3: Entry 8 of 50 File: USPT Feb 27, 2001

US-PAT-NO: 6194562
DOCUMENT-IDENTIFIER: US 6194562 B1

TITLE: Endotoxin reduction in nucleic acid purification

DATE-ISSUED: February 27, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Smith; Craig E.	Oregon	WI		
Creswell; Donald A.	Cottage Grove	WI		
Bitner; Rex M.	Cedarburg	WI		
White; Douglas H.	Madison	WI		
Butler; Braeden L.	Madison	WI		
Lesley; Scott A.	Oregon	WI		

US-CL-CURRENT: 536/24.5; 435/320.1, 536/25.41, 536/25.42

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw Desc | Image

☐ 9. Document ID: US 6190642 B1

L3: Entry 9 of 50 File: USPT Feb 20, 2001

US-PAT-NO: 6190642
DOCUMENT-IDENTIFIER: US 6190642 B1

TITLE: Irrigating and lavage compositions

DATE-ISSUED: February 20, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Dougherty; Emery W.	York	PA		
Heyde; John B.	York	PA		

US-CL-CURRENT: 424/49; 424/54, 424/55, 433/216, 433/86

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw Desc | Image

☐ 10. Document ID: US 6180596 B1

L3: Entry 10 of 50 File: USPT Jan 30, 2001